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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-------------------------------------------------------|--------------------|----------------------|-----------------------------------------------------|-------------------------------------------|
| 10/593,659 | 10/22/2007 | James Hardwick | 21412YP | 1323 |
| 210 MERCK P O BOX 2000 RAHWAY, NJ 07065-0907 | 7550 07/29/2010 | | <div>EXAMINER</div> <div>WESSENDORF, TERESA D</div> | |
| | | | <div>ART UNIT</div> <div>1639</div> | <div>PAPER NUMBER</div> |
| | | | <div>MAIL DATE</div> <div>07/20/2010</div> | <div>DELIVERY MODE</div> <div>PAPER</div> |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/593,659

Applicant(s)

HARDWICK ET AL.

Examiner

TERESA WESSENDORF

Art Unit

1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 4/29/10.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-16 is/are pending in the application.
- 4a) Of the above claim(s) 7-16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 21 September 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/CG-706)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____
- Paper No(s)/Mail Date 9/21/06, 7/21/08, 4/29/10

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-7 (not 11-7, as stated at page 2 of the REMARKS) in the reply filed on 1/15/10 is acknowledged. The traversal is on the ground(s) that a search of the Group I claims would of necessity, include a search of the Group II and III claims since these relate to the use of a nucleotide sequence. Consequently, these groups should be combined. As such, no savings of PTO resources will be achieved by enforcing the election/restriction requirement presently asserted. This is not found persuasive because the method steps of group I are distinct from that of the method steps of group II comprising screening a plurality of therapeutic agents. The method steps of group I relate only to determining the proliferative status of a population of endothelial cells and not to its therapeutic effect or results. Thus, each of group I and group II contain distinct process steps. Group III is drawn to a compound containing array which differs in composition from each other as shown by the different claimed Tables containing different biomarkers. Accordingly, it would be a burden to examine a method wherein the compounds are so diverse and distinct from one another. Furthermore, the search extends to the different commercially available

databases. The search is not co-extensive with patents (US and foreign patents) search. Also, the patentability determination for each of the distinct inventions is different for each of the different given statutes. A prior art reference anticipating the method of e.g., Group I would not anticipate or render obvious the method of group II or composition of array containing different gene biomarkers.

The requirement is still deemed proper and is therefore made FINAL.

Species Election/Restriction

Applicants' election of the species genes exemplified in Table 3 and the patient being treated with a KDR kinase inhibitor as detailed in claim 6 is also acknowledged. Further election with traverse of the species Angpt2 filed on 4/29/10 is also acknowledged. The traversal is on the ground that the gist of the invention is the identification of one or more genes (gene signature) informative of the proliferative status of endothelial cells. Thus, choosing or being forced to choose one gene from a collection that may constitute a signature may be unfair to the spirit of the claimed invention. Applicants' request reconsideration of the election requirement.

In view of applicants' request the election of species with respect to a single species is reconsidered and withdrawn. The species contain in Table 3 as elected above would be examined.

Claims 7-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions and species, there being no allowable generic or linking claim.

Status of Claims

Claims 1-16 are pending.

Claims 7-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and species.

Claims 1-6 are under examination.

Abstract

The abstract of the disclosure is objected to because it uses the PCT abstract. Correction is required. See MPEP § 608.01(b).

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Please see page 19, line 17 and 30, for example. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Appropriate correction is required.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors (typographical, grammatical and idiomatic). Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Information Disclosure Statement

The listing of references in the specification at e.g., pages 79-80 is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

1. Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claim method for determining the proliferative status of a population of endothelial cells is drawn to a non-statutory subject matter. This method does not fall within the above categories of process of using or making. To profile a proliferative signature of a cell as endothelial is not a method of making the compound or using a compound. Rather, it is merely gathering information as to e.g., its gene components.

2. Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility.

There is no specific or substantial utility for the claimed method of determining the expression profile of an endothelial cell or genes of the expression profile produced by the method.

Tables 3-6 provide the various gene biomarkers that can bind to alleged proliferative genes in the endothelial cell. But it is not apparent as to the genes in a sample containing endothelial cells that bind to the biomarkers in the array or the function of the genes that bind to the biomarker. Applicants have no working example indicating that the genes of the expression profile obtained have any activity except for the alleged binding to the biomarker array. An expression profile having no [transcription factor] activity or other unique characteristics would not be useful to one skilled in the art.

Since every gene has a binding activity, it is unclear how the gene expression profile can be used to achieve any real-world context of use. While having the ability to regulate (bind) expression of a gene at its proliferative stage(s) may be useful, further guidance is necessary as to what gene(s) are expressed, and how such expression would ultimately result in a useful outcome. What real world use would an expression profile of endothelial cells expressing numerous unknown or undisclosed genes have? It is apparent that further research is required before the claimed genes would be of benefit to the public. The courts have decided that a utility which requires or constitutes carrying out further research to identify or reasonably confirm

a "real world" context of use lacks specific and substantial utility.

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point--where specific benefit exists in currently available form--there is insufficient justification for permitting an appellant to engross what may prove to be a broad field." (*Brenner v. Manson*, 383 U.S. 519 (1966)).

Thus, while regulating the expression profile of certain endothelial cells would provide substantial benefit to the public, the claimed invention is not refined and developed to the point where specific benefit exists. There is no guidance provided as to how the genes should be used to regulate tumor in a manner to achieve a useful outcome. Accordingly, the claimed invention lacks substantial asserted utility.

There is also no well-established utility for the gene expression profile to inhibit tumor growth. The heterogeneity of endothelium from different vascular beds is well known and the difficulty in extrapolating from the study of one endothelial cell type to another. The genes from the expression profile do not have a well-established utility for inhibiting tumor. Thus, for the reasons set forth, the claimed invention lacks utility under current utility guidelines. (see Utility Examination

Guidelines published in Federal Register/ Vol. 66, No. 4/
Friday, January 5, 2001/ Notices; p. 1092-1099).

Claims 1-6 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps that results in

the "expression profile". The preceding steps recite only for providing of an array and contacting of a sample containing endothelial cells with the array. Thus, it is vague and indefinite as to how the "expression" occurs given no antecedent from the preceding steps.

2. Claim 1 is vague and indefinite as to the "rate" of proliferation of the endothelial cells. The degree or basis of said proliferation rate is indefinite i.e., how much or how fast etc. the rate is measured or occurred. This is also inconsistent with the preamble recitation of the proliferative "status".

3. Claim 2 is vague and indefinite as to the reference to a gene. The base claim 1 does not recite gene(s). The term "one or more" covers an infinite amount. "At least one" is suggested.

4. The used of acronyms in claim 3 for the different genes is indefinite. It is suggested that the full names of each acronyms be provided.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

I. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al (Angiogenesis 3,211--219, 1999).

For claim 1, Zhang discloses throughout the article at e.g., a method for determining the proliferative status of a population of endothelial cells comprising providing an array comprising a substrate, having a plurality of addresses (Zhang at e.g., abstract, page 211) , wherein each address has disposed thereon a capture probe or

oligonucleotide that can specifically bind an endothelial cell proliferative biomarker (Zhang at e.g., page 211, col. 2, "commercial filters with 588 cDNAs of known sequence and 9 housekeeping genes (Fig. 2a); b) preparing a nucleic acid test sample from a population of endothelial cells(see Zhang at e.g., page 212, col. 1, Materials and methods section); c) contacting the nucleic acid sample with the array (see page 212, col. 2; differential hybridisation of cDNA expression arrays, the 3~P-labelled single-stranded cDNA probes prepared from proliferating and quiescent HDMECs were separately hybridized in hybridization solution to a pair of identical commercial filters); and d) determining an expression profile by detecting binding of the nucleic acids in the test sample to each address of the plurality of addresses present on the array, thereby determining the proliferative rate of the endothelial cells(see e.g., page 213, col. 1, Results section, Expression of mRNAs in quiescent and EGF-stimulated proliferating endothelium. Tables 1 and 2 documents the expression profiles of 9 house keeping genes).

For claim 2, Zhang discloses the different genes in Table 2, page 216.

II. Claims 1-6 are rejected under 35 U.S.C. 102(a) as being anticipated by Favre et al (Am. J. Physiol. Heart Circ. Physiol. 285: H1917-H1938, 2003.)

For claim 1, Favre et al disclose throughout the article at e.g., page H1918, col. 1, a method of profiling gene expression in endothelial cells where RNA from freshly isolated endothelial cells are analyzed on oligonucleotide microarrays covering tens of thousands of genes or expressed sequence tags (ESTs)(biomarkers, as claim).

For claims 2-3, Favre teaches at e.g., pages H1927 Table 5, including the genes Angpt2, Endrb and etc. through Table 6, H1929.

For claim 4, Favre teaches at e.g., paragraph bridging pages H1930-31, sample containing endothelial cells isolation from tumor.

III. Claims 1 and 4-6 are rejected under 35 U.S.C. 102(b) as being anticipated by DiPrimo et al (BMC Cancer 2003, 3, 1-12).

DiPrimo discloses throughout the article at e.g., page 1, abstract methods for expression profiling using microarrays applied to peripheral blood mononuclear cell (PBMC) samples obtained from patients with advanced colorectal cancer. The PBMC samples were harvested pre-treatment and at the end of the first 6-week cycle from patients receiving standard of care chemotherapy or standard of care plus SU5416, a vascular endothelial growth factor (VEGF) receptor tyrosine kinase (RTK) inhibitor. Results from matched pairs of PBMC samples from 23 patients were queried for expression changes that consistently correlated with SU5416 administration. See also page 11, col. 1.

Claims 1-6 are rejected under 35 U.S.C. 102(e) as being anticipated by Mor et al (USP 7666583).

Mor discloses throughout the patent at e.g., col. 2, lines 26-31, a method comprising comparing the expression of two or more biomarkers, wherein the diagnosis of cancer is made by comparing the expression profile of said two or more biomarkers to a predetermined standard profile for said biomarkers, and wherein a difference in the profiles diagnoses or aids in the diagnosis of cancer.

FIG. 2 is a schematic representation of a sample protein microarray slide with 16 subarrays. Subarrays refer to the 16 wells, or circular analysis sites, on the slide. Array refers to the antibody content printed in a well.

Mor at e.g., paragraph bridging col. 1 and col. 2 disclose the biomarkers as selected from the group consisting of: 6Ckine, ACE, BDNF, CA125, E-Selectin, EGF, Eot2, ErbB1, follistatin, HCC4, HVEM, IGF-II, IGFBP-1, IL-17, IL-1srII, IL-2sRa, leptin, M-CSF R, MIF, MIP-1a, MIP3b, MMP-8, MMP7, MPIF-1, OPN, PARC, PDGF Rb, prolactin, ProteinC, TGF-b RIII, TNF-R1, TNF-a, VAP-1, VEGF R2 and VEGF R3. see further Table 2.

It is considered that the expression profile of the cancer containing endothelial cells have been determined given its use to diagnose cancer.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Baker et al (USP 7081340) teaches a method of gene expression profiling based on hybridization analysis of polynucleotides.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA WESSENDORF whose telephone number is (571)272-0812. The examiner can normally be reached on flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TERESA WESSENDORF/

Primary Examiner, Art Unit 1639